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Acute and longer-term outcomes using ketamine as a clinical treatment at the Yale Psychiatric Hospital

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Abstract

Introduction: Ketamine has emerged as a rapid-acting antidepressant, though controversy remains regarding whether sufficient data exist to justify its use outside of research protocols. In October 2014, our institution began providing ketamine as an off-label therapy for patients not able to participate in research protocols on a case-by-case basis. Here we describe our experience over 30 months providing ketamine as a clinical treatment to participants with severe and treatment-resistant mood disorders.

Method: Initially, patients were treated with a single- or double-infusion protocol (0.5mg/kg over 40 minutes intravenously). We later transitioned to a 4-infusion protocol over two weeks.

Results: Overall, 54 patients have received ketamine at our institution, with 518 total infusions performed. A subset of 44 patients with mood disorders initiated the four-infusion protocol, of which 45.5% responded and 27.3% remitted by the 4th infusion. A subsample (N=14) have received ketamine on a long-term basis, ranging from 12 to 45 total treatments, over a course of 14 to 126 weeks. We found no evidence of cognitive decline, increased proclivity to delusions, or emergence of symptoms consistent with cystitis in this subsample.

Conclusion: In general, ketamine infusions have been tolerated well. The response and remission rates in our clinical sample were lower than those observed in some research protocols. The small number of patients who have been treated on a maintenance schedule limits the conclusions that can be drawn regarding long-term safety of ketamine, however no long-term adverse effects have been observed in our sample.

Introduction:

Several small, clinical trials have shown that sub-anesthetic doses of ketamine have rapid-acting antidepressant effects in patients with treatment-resistant mood disorders.[1–5] Additional studies suggest the relative safety of repeated (up to 6) doses.[6–10] Due to the great unmet need for improved therapeutics in treatment-resistant mood disorders, the off-label clinical use of ketamine for the treatment of psychiatric disorders has grown rapidly since 2012.[11] Nonetheless, controversy remains about whether ketamine should be used

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outside of research protocols due to concerns regarding potential negative clinical outcomes from repeated use, including impaired cognition, delusions, and interstitial cystitis.[12–15] In October 2014, our institution began providing ketamine as an off-label therapeutic agent on a case-by-case basis for patients who were unable to participate in ongoing research protocols. This manuscript describes our experience over 30 months of providing ketamine as a clinical treatment to participants with severe and treatment-resistant mood disorders.

Methods and Clinical Protocol:

Ketamine treatments, as part of the Interventional Psychiatry Service at Yale Psychiatric Hospital, are given in an electroconvulsive therapy suite. After psychiatric consultation, signed informed consent (See Supplemental Information) and medical clearance (including basic lab work, urine toxicology, electrocardiogram, and history and physical examination), patients began intravenous infusions. As emphasized in the written consent form, patients understood that this treatment was not approved by the Food and Drug Administration and was given off-label for depression.

Patients were instructed to fast for approximately 8 hours (starting at midnight) prior to each infusion. Upon the patient's arrival to the treatment suite, baseline blood pressure, heart rate, pulse oxygenation, respiratory rate, and temperature were recorded and a peripheral intravenous (IV) catheter inserted. Ketamine was dosed at 0.5mg/kg (based on standard research protocols[4, 16]), mixed in 500cc of 0.9% normal saline and infused over 40 minutes. For patients with a body-mass index ≥ 30, we initially adjusted the dose based on ideal body weight (see eAppendix 1). During the infusion, blood pressure was monitored at least every 10 minutes, and heart rate and pulse oxygenation were monitored continuously. We continued to monitor vital signs every 10 minutes following the completion of the infusion. If nausea occurred during or shortly after an infusion, we offered patients intravenous ondansetron prophylactically at the next infusion. Psychotropic medications were not controlled and washouts were not done routinely prior to initiation of therapy. In general, we avoided use of benzodiazepines in the 8–12 hours prior to dosing, based on theoretical concerns[17] and limited prior evidence suggesting an attenuation of ketamine's antidepressant effects when given concomitantly with benzodiazepines.[18] Patients were instructed to hold psychotropic medications until after ketamine on the days of treatment, but were instructed to take other medications (i.e., for blood pressure, heart rate, diabetes, etc.) prior to dosing.

Initially, patients were treated with a single- or double-infusion protocol (one or two doses over one week). In early 2015, as several studies emerged showing the safety of a multiple-infusion protocol,[6, 8, 9] we transitioned to a four-dose protocol given twice per week. We based this protocol on evidence presented at professional meetings in 2014 that showed that thrice weekly was no better than twice weekly dosing.[8]

Initially, symptom severity was tracked with the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) scale,[19] which was administered at each visit. In addition, a QIDS-SR scale was given to outpatients to fill out 24 hours following each infusion. The Clinician-Administered Dissociative State Scale (CADSS)[20] was performed at

the completion of each infusion (40 minutes) as well as immediately prior to discharge (to ensure discharge readiness criteria) or return to the inpatient unit. As the service grew, we implemented the Montgomery-Åsberg Depression Rating Scale (MADRS)[21] to track outcomes at each visit prior to treatment.

The service has treated both inpatients and outpatients. Similar to our ECT guidelines, outpatients were not permitted to drive on days of infusion and were discharged to the care of a responsible adult. Criteria for discharge readiness were 1) a return to pre-dose hemodynamic parameters, 2) a CADSS score of 0 (or equal to or below pre-treatment score), and 3) at least 30 minutes of observation following the completion of the infusion. Institutional Review Board granted a waiver of full review for a medical record review. Yale-New Haven Hospital approved the written consent form (eAppendix 2).

For patients with meaningful clinical improvement, we attempted to maintain this improvement using various pharmacologic or psychotherapeutic strategies based on individual treatment history. A portion of the patients treated (n=16) have undergone open-label cognitive behavioral therapy in an effort to sustain ketamine's antidepressant effects, the results of which have been published previously.[10] For patients who have been unable to sustain response, we have provided continuation/maintenance ketamine treatments with ongoing informed consent of the risks and benefits of continued treatment. We have instituted a flexible, symptom-triggered tapering schedule, which we modeled after a continuation/maintenance ECT schedule.[22] We attempted to spread the frequency of treatments to every 3 or 4 weeks, while still maintaining response.

There is concern for cognitive deterioration with repeated exposure to ketamine.[13] Consequently, we have instituted regular cognitive assessments for all patients who receive ketamine in our program. We used the CogState battery (www.cogstate.com), which includes tasks assessing attention, working memory, visual memory, processing speed, and verbal memory with delayed recall. Further description of these tasks can be found elsewhere.[23, 24] Cognitive assessments are done at baseline and thereafter every 6–12 treatments. A subsample of our cohort (N=14) have received ketamine for at least 14 weeks. Because the patients in this ongoing cohort have received a differing number of treatments to date, we approached this analytically by correlating the total number of treatments with the paired difference (age-adjusted z-score) of the first and most recent cognitive assessments.

Results:

In total, 54 patients were treated with one or more ketamine infusions from October 2014 through February 2017. In total, 518 infusions were given. Table 1 shows the demographic and baseline clinical characteristics of these patients. Three patients with schizoaffective disorder were treated. The rationale for one of these patients has been described previously.[25, 26] The other two patients had failed ECT and were suffering from severe functional limitations due to the current depressive episode.

Outcomes following acute treatment period

Of 54 total patients treated, 44 patients had a primary mood disorder and began a 4-infusion protocol, with treatment given twice weekly over 2 weeks. Using a self-report measure (QIDS-SR), patients showed a significant reduction in symptoms over time in a general linear, mixed model (main effect of time, $t=-9.40$, $p<0.001$; Figure 1). Overall, QIDS-SR scores decreased from 16.8 to 10.4, a 37.9% reduction. The majority of the improvement (64.7% of total improvement, or a reduction of 4.12 QIDS-SR points) occurred between the first and second infusions (a 2–4 day time-period). MADRS data was collected on 36 of these subjects and showed a similar pattern (Figure 1), with a significant effect of time in a general linear, mixed model ($t=-8.48$, $p<0.001$). Overall, MADRS scores decreased from 32.8 to 20.4, a 37.8% reduction. The majority of improvement (68.5% of total improvement, or a reduction of 8.5 MADRS points) occurred between the first and second infusions. Using a general linear, mixed model, we adjusted for peak CADSS (at 40 minutes), age, gender, and history of failed ECT. None of these variables moderated the effect of time using the MADRS or QIDS scores.

Dichotomous Outcomes

We calculated dichotomous outcomes from the sample of patients with mood disorders who began a 4-infusion protocol (N=44). Following the first infusion, 31.7% of patients were classified as responders (50% or greater improvement in QIDS-SR). By the 4^{th} infusion, 45.5% of patients were responders. Prior to our instituting a 4-infusion protocol, we treated 6 patients with mood disorders with single- or double-infusion protocols. Of these 6, 5 experienced a 50% improvement in mood symptoms following the first treatment. Hence, 50.0% of patients with mood disorders responded to a protocol of infusions ranging from 1 to 4. Following a single infusion, 11.3% of patients were classified as remitters (QIDS-SR $\leq$ 5); following 4 infusions, 27.3% of patients were classified as remitters.

Using MADRS data on a smaller sample (N=36), 22.2% of patients responded following the first infusion. By the 4^{th} infusion, 38.9% responded. We did not perform MADRS assessments for the 6 patients with mood disorders treated before we instituted a 4-infusion protocol. Following a single infusion, 13.9% of patients remitted (MADRS $\leq$ 10); by the 4^{th} infusion, 25.0% of patients remitted.

Discontinuation of Acute-Phase Treatment

Of the 44 patients with mood disorders who began the 4-infusion protocol, 5 did not complete all treatments. Reasons for discontinuation were lack of efficacy (4) and lack of tolerability of infusions (1). Of the 518 total infusions (N=54), two were discontinued mid-infusion. In a 48-year-old female with MDD, type I diabetes and hypertension, the first infusion was stopped early due to elevated blood pressure (max 181/72). Within 10 minutes of stopping the infusion, blood pressure was 168/69, and by 30 minutes was 149/64. This subject received low-dose oral labetalol (50–100mg) pre-treatment prior to subsequent infusions with good effect (max blood pressures of 161/79, 141/61, and 152/69 for the 2^{nd}, 3^{rd}, and 4^{th} infusions, respectively). The subject experienced a remission following the first infusion. The other early termination occurred during the first infusion of a 78-year-old female with MDD who was hospitalized. The infusion was stopped 10 minutes early due to

intolerable dissociative side effects. The patient was able to tolerate all 3 subsequent infusions but did not show clinical improvement. Of the 54 patients who received ketamine, 16 (29.6%) experienced mild nausea and received prophylactic ondansetron for subsequent infusions. No patient vomited during treatment. Two patients (3.7%) received pre-treatment, low-dose oral labetalol prophylactically based on blood pressure elevations during prior treatments.

Long-term outcomes

Figure 2 shows long-term outcomes over two years for all patients (N=14) from our program who have received continuation/maintenance ketamine treatments for at least 14 weeks.[27] Overall, these patients have received 351 treatments, with an average treatment per patient of 25.1 (SD 10.5) and a median per patient treatment of 27 (range 10–45). The average length of course of therapy among these patients is 75.7 (SD 39.2) weeks, with a median of 84 weeks (range 14 – 126). Of these 14 patients, 3 initiated therapy on a single- or double-infusion protocol. Not including acute course of four treatments given twice per week, the average time between treatments is 22.3 (SD 22.7) days, with the median time between treatments of 21 days (range 2–189). Among the 14 longer-term patients, we observed 1 case of tachyphylaxis. A 16-year-old male with MDD who failed ECT and had recurrent hospitalizations showed remission following four treatments (MADRS was 4 at this time point). After attempting to taper the treatments to every 2 weeks, his MADRS rose to 28. Additional infusions given twice weekly did not lead to clinical improvement. Two patients relapsed resulting in suicide attempts and hospitalizations during long-term follow up. Both were able to regain response status after repeated ketamine course (infusions twice weekly). Seven additional patients relapsed (depression score <25% improvement from baseline) during the two-year follow-up period but were all able to regain response status. One patient relapsed after a 6-month hiatus (living in another state) and was able to regain a partial but not full response to treatment after a repeat acute series of ketamine treatments. Three patients did not relapse during longer-term follow-up. Qualitatively, 7 of these long-term patients report that the antidepressant effect of ketamine starts to fade approximately 3 weeks following exposure.

Concomitant Medications

Among the full sample, the majority of patients (96.3%) were taking one or more psychotropic medications (eAppendix 3). The most common medication type was an antidepressant, taken by 72.2% of patients. This was followed by antipsychotic (53.7%), sedative/hypnotic (50.0%), mood stabilizer/anticonvulsant (37.0%), stimulants (22.2%), and lithium (18.5%). There was no moderating effect of any class of psychotropic medication, including benzodiazepines, on antidepressant effect as measured by MADRS or QIDS-SR. Among the 14 longer-term patients, changes in concomitant medications can be found in the eAppendix 4.

Safety

One of our patients, an adolescent with multiple hospitalizations who failed ECT prior to beginning ketamine, was surreptitiously using cannabis on a frequent basis. He had a history of intermittent cannabis use prior to beginning treatment though this was not disclosed. His

urine toxicology screen prior to initiating therapy was negative. Upon discovery of his use, further ketamine treatments were contingent upon his abstinence, which he was not able to maintain. Hence ketamine treatments were discontinued.

Two patients who received treatment later committed suicide. One experienced significant clinical improvement after 4 treatments given over 2 weeks. She received one maintenance treatment 2 months following the acute course of treatments but no further ketamine treatments following this. She committed suicide by hanging 4 months after her last dose of ketamine. Another patient committed suicide by hanging approximately 10 months after receiving his final ketamine treatment. He had been seen in psychiatric follow up the week of his death and had been in a heated argument with an ex-spouse the day of his suicide. He had experienced a partial improvement from the ketamine following 4 treatments (35.6% improvement).

Acute Dissociative Effects

Following the first treatment, the mean CADSS scores at 40 minutes was 6.79 (SD 8.51), and had nearly returned to zero at 70–80 minutes (mean score 0.12, SD 0.32). Following the 2^{nd}, 3^{rd}, and 4^{th} infusions, CADSS scores at 40 minutes were 5.86 (SD 6.25), 4.52 (SD 5.03), and 4.53 (SD 7.16), respectively. Following the 2^{nd}, 3^{rd}, and 4^{th} infusions, mean CADSS scores at 70–80 minutes were 0.07 (SD 0.26), 0.04 (SD 0.19), and 0.00 (SD 0.00), respectively.

Vital Sign Monitoring

Collapsing data across the 4 acute infusions, mean systolic blood pressure (SBP) increased from baseline of 123.3 (SD 16.6) to a peak of 133.5 (SD 19.0) at 50 min (10 min following completion of infusion). By 70 min, mean SBP was 127.9 (SD 15.6) (Figure 3). Mean diastolic blood pressure (DBP) increased from 73.8 (SD 9.6) at baseline to a peak of 77.6 (SD 10.8) at 40 min. By 70 min, mean DBP was 75.6 (SD 12.5). Mean heart rate remained between 75 and 78 beats per minute (SD 13.3–13.8) throughout the infusion and recovery time. Mean pulse oximetry readings ranged from 98.1–98.4% (SD 1.5–2.0) throughout the infusion period and recovery time. Five patients experienced SBP elevated over 180 during their first infusion, though 4 of these were transient. One patient consistently had a SBP of 180 or greater at the last time point (40 minutes) of his second, third, and fourth infusions, which normalized within 30 minutes following treatment. During the first infusion, one patient transiently had a DBP of 110, which normalized within 30 minutes post-infusion. No patient had DBP values of 110 or greater during the second, third, or fourth infusions.

Cognitive Outcomes

Among the subsample of patients receiving ketamine long-term (N=14), there was no correlation between number of treatments received and paired change in cognitive measures of attention, processing speed, working memory, verbal memory, and visual memory (Table 2). The average paired difference for each domain was positive, except for the measure of attention. The median time between assessments was 331 days (range 49–522 days). Among the full sample, baseline measures of cognition did not correlate with improvement in depressive symptoms.

Discussion

From October 2014 through February 2017, our service provided ketamine as a clinical treatment to 54 patients, 14 of whom have received long-term infusions of 12 treatments or more. Infusions given at 0.5mg/kg over 40 minutes are generally well tolerated, with one patient requiring premature cessation of infusion prior to completion due to intolerable dissociative effects, and one for transient hypertension. Notably, our response (50%) and remission (27.3%) rates following a 4-infusion protocol are lower than those reported in most clinical trials.[1, 3–5, 9] We found no effect of acute dissociative symptoms, age, gender, and history of failed or inability to tolerate ECT on response. Among the subsample receiving long-term treatment, there was no correlation between number of infusions and change in cognition.

Many potential reasons exist for the discrepancy between the relatively lower rates of response and remission in this sample compared to research settings. There is often an "efficacy-effectiveness" gap as new treatments move from research to clinical settings.[28] Considerably less attention is paid to patients outside of research protocols compared to research subjects. Part of the large effect of ketamine observed in research trials may be due to these non-specific, supportive effects. Randomized trials with ketamine compared to saline placebo may also result in artificially large effect sizes due to functional unblinding because of psychoactive properties of the drug. Compared to samples from prior research trials, our patient sample may also represent a more ill and complicated population. As noted above, most of the subjects receiving open-label clinical treatment in our program were considered for clinical trial enrollment but were not appropriate for participation for various reasons, including disallowed comorbid conditions (general medical and/or psychiatric), evidence of ultra-refractoriness (failing numerous previous treatment trials and/or ECT), current hospitalization, inability to delay treatment long enough to complete required study procedures (medication washout, observation periods), presence of significant suicidal ideation or behavior, and age outside of protocol limits. As one example, almost 40% of our patients began treatment as inpatients. Whereas some research protocols required patients to be hospitalized overnight as part of the research protocol,[1, 29] the hospitalized patients from our sample were admitted for clinical reasons of suicide risk or inability to function. Nonetheless, in this sample of complicated and severely ill patients (55.1% who had failed or not tolerated ECT and 38.9% who were inpatients), we feel a 50% response rate within 2 weeks of treatment is a significant outcome.

While we did not document potential adverse events with the same level of scrutiny afforded in sponsored clinical trials, we did not observe gross decrements in cognition, an increased propensity for delusions, or emergent symptoms indicative of cystitis over time. Beyond the one adolescent with continued cannabis use, we saw no evidence of patients showing signs of substance abuse or increased drug seeking in our sample of patients. It should be emphasized, however, that our sample of patients receiving long-term treatment (N=14) is very small and does not provide statistical power sufficient to detect subtle changes in cognition, delusions, or bladder function. The field urgently awaits further and more powerful long-term safety data on ketamine and related compounds.

Overall, in the 30-month history of our program, two former patients committed suicide. One did so 10 months following last contact with our program and was judged not to be related to ketamine treatment. The other suicide occurred 4 months following last contact with our program. In this case, the patient's health maintenance organization did not refer the patient back to our institution for consideration of further treatment. Both of these patients had a history of hospitalization for suicide attempts. It noteworthy that almost half (46.9%) of the patients in our sample had a history of attempted suicide while nearly two-thirds (64.8%) had been hospitalized for suicidal ideation or suicide attempts. In light of this, we believe it is unlikely that ketamine exposure increased their propensity towards suicide, especially given the long period between the time of death and last ketamine exposure. However, given the severity of illness of patients with treatment-resistant depression,[7] these cases highlight the critical need for consideration of longer-term strategies prior to treatment initiation, especially given the lack of long-term data on ketamine use.[30, 31]

The small size and racial homogeneity of our sample limits the generalizability of our results. However, given the paucity of data on long-term safety, our results provide the first signal of long-term safety in a small sample. There remains an urgent need for more powerful and comprehensive long-term safety data on ketamine from much larger samples. This need is underscored by the rapid growth in the number of providers offering ketamine outside of research protocols for the treatment of psychiatric disorders.[11] Given that racemic ketamine hydrochloride no longer has patent protections, it is unlikely that large and long-term clinical trials will be conducted to provide such long-term safety data. The formation of a registry combining data from community and academic sites is therefore the most realistic way of capturing long-term data on the effectiveness and safety of ketamine as a treatment for mood disorders.[32]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Points

- Ketamine shows promise as a potential treatment for refractory mood disorders; however, evidence to date are mostly limited to short-term outcomes (≤1 month)
- The field urgently awaits long-term data on efficacy and safety of ketamine as a treatment for psychiatric disorders
- Longer-term treatment strategies should be considered prior to initiation of ketamine as a treatment

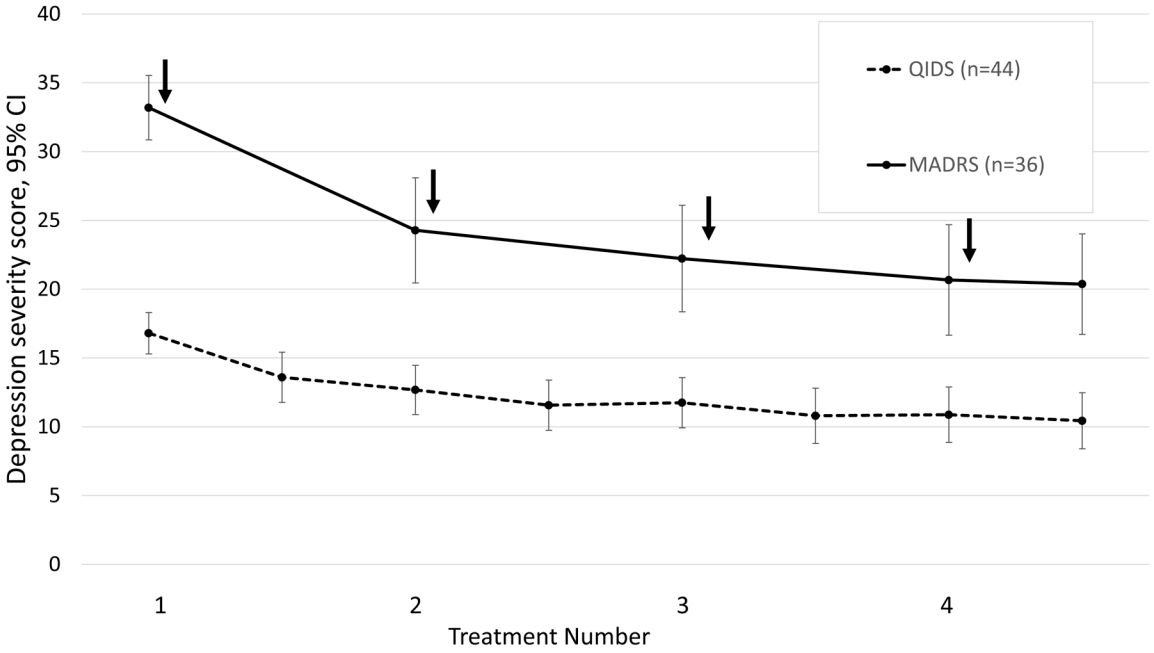

Figure 1.

Depression severity over time in a four-infusion ketamine protocol, last observation carried forward (LOCF) for missing data. A mixed-effects, general linear model showed a main effect of time using the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR, main effect of time, $t=-9.72$, $p<0.001$) as well as the Montgomery-Asberg Depression Rating Scale (MADRS, $t=-8.48$, $p<0.001$). Treatments were given twice weekly. Time points between treatments are 2–4 days; a QIDS-SR was administered 24-hours following each treatment. Error bars are 95% confidence intervals. Arrows indicate ketamine infusions.

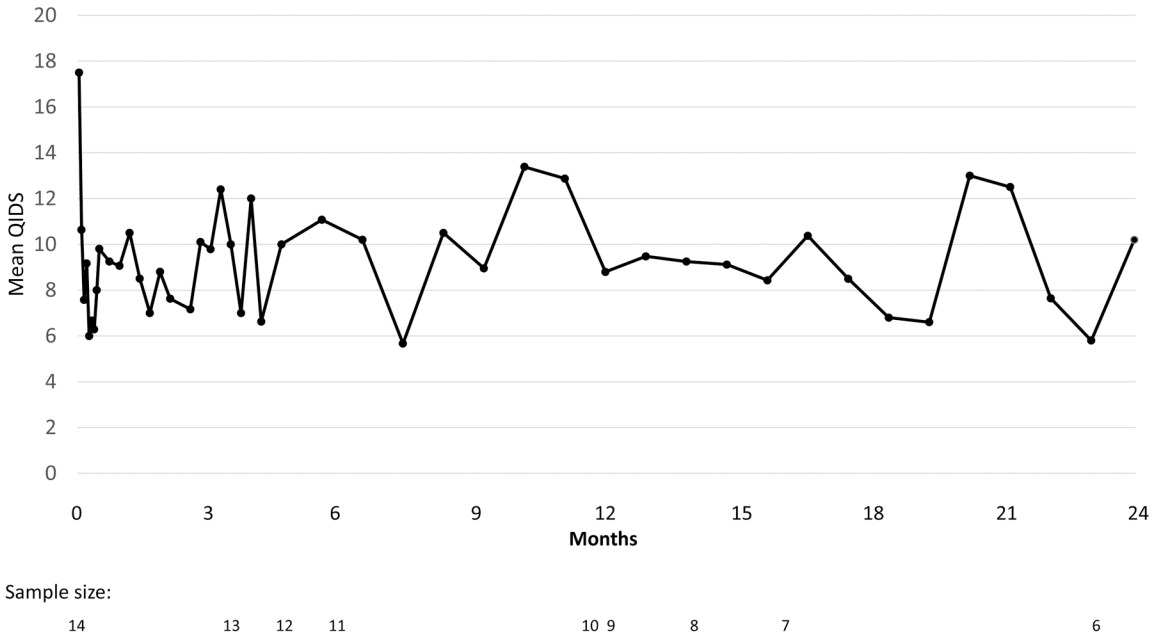

Figure 2.

Longer term outcomes of patients who have received continuation/maintenance ketamine treatment (n=14). The sample size decreases over time, reflecting where patients are in their current treatment and does not indicate that they have dropped out of treatment.

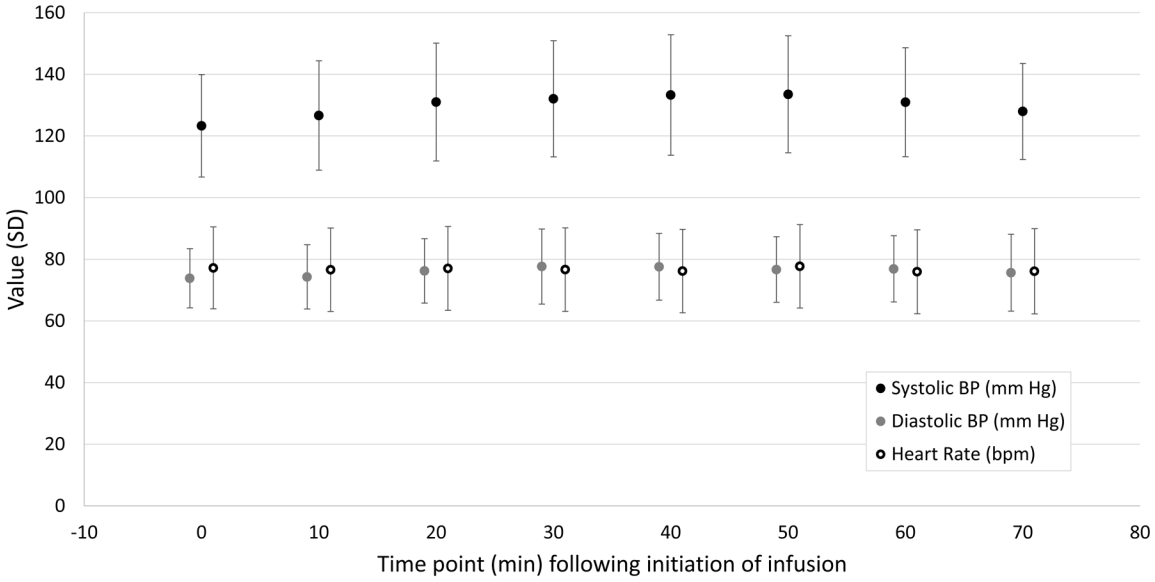

Figure 3.

Vital sign monitoring during and 30 minutes following a 40-minutes infusion protocol of 0.5mg/kg intravenous ketamine. Data represent 54 patients, with 210 total infusions.

Table 1.

Demographic and clinical characteristics (N=54).

Variable	N/Mean (%/SD)
Age (SD)	46.7 (18.0), range 16–87
Male n (%)	21 (38.9)
Marital Status n (%)	
Single	25 (46.3)
Married	18 (33.3)
Divorced/Separated	5 (9.3)
Other	6 (11.1)
Disabled, n (%)	2 (4.7)*
Race n (%)	
White	52 (96.3)
African American	1 (1.9)
Other	1 (1.9)
Diagnosis n (%)	
Major Depressive Disorder	44 (81.5)
Bipolar Disorder	6 (11.1)
Schizoaffective Disorder	3 (5.6)
Catatonia	1 (1.9)
History of Electroconvulsive Therapy, n (%)	27 (55.1)
History of Hospitalization, n (%)	40 (74.1)
History of Hospitalization for Suicidal Ideation or Attempt, n (%)	35 (64.8)
History of Suicide Attempt, n (%)	23 (46.9)**
Inpatient Status at First Infusion, n (%)	21 (38.9)
Baseline QIDS-SR Score (SD)	19.8 (6.0)
Baseline MADRS Score (SD)	33.1 (6.9)

QIDS-SR - Quick Inventory of Depressive Symptomatology-Self Report; Montgomery-Asberg Depression Rating Scale; Missing data for 11* and 5** patients

Table 2.

Cognitive outcomes of long-term ketamine treatment (N=14). Paired differences between the first and most recent cognitive assessments were calculated for each subject, then correlated with the total number of treatments between assessments. A positive difference indicates improved performance at second assessment compared to baseline. Tasks included are: an Identification Task (attention), a One-Back Task (working memory), One Card Learning Task (visual memory), International Shopping List and Delayed Recall (verbal memory, with delayed recall); and Detection Task (processing speed). Further description of these tasks can be found elsewhere.[23, 24]

Cognitive domain	Mean paired difference between first and most recent cognitive assessment (age-adjusted z score)	Correlation between paired difference (age-adjusted z score) and number of ketamine treatments	
		r^2 value	p value
Processing speed	0.330	0.035	0.538
Attention	−0.187	0.042	0.500
Visual memory	0.126	0.008	0.771
Verbal memory	0.361	0.021	0.635
Verbal memory, delayed recall	0.316	0.099	0.297
Working memory	0.807	0.143	0.203